Scientific Abstract

The basis for this phase I trial of ALVAC-hB7.1 is the hypothesis that despite expression of a number of potential tumor regression antigens, melanoma cells fail to initiate anti-tumor immune responses due in part to a lack of appropriate T cell costimulation. Thus, transfection of melanoma cells within tumor nodules with the B7.1 cDNA may provide the necessary costimulatory signal to prime anti-tumor immune responses and generate effector T cells capable of recognizing non-transfected tumor cells remote from the injection site. In light of considerable clinical experience with the ALVAC vector demonstrating no significant toxicity and the seemingly remote potential for toxicity related to intratumoral expression of B7.1, we propose to examine a single dose of ALVAC-hB7.1 administered intratumorally twice weekly for two weeks. We propose a dose of 2.5×10^9 pfu of ALVAC-hB7.1 because this is the highest dose which can be delivered in a reasonable volume for intralesional injection based upon the infectious titer of the GMP product. If the proposed dose of ALVAC-hB7.1 delivered to a single lesion is well tolerated in an initial group of 6 patients, we propose to deliver a combination of this dose of ALVAC-hB7.1 and the maximum feasible dose of ALVAC-hIL-12 ($1\text{-}2 \times 10^6$ $TCID_{50}$) into each of one to two tumor nodules in a group of 6 patients. The hypothesis underlying the addition of ALVAC-hIL-12 is that the local production of IL-12 in melanoma nodules can alter the tumor cell environment by enhancement of immune effector cell functions, induction of gamma interferon and production of a more effective anti-tumor immune response by expansion of a T-helper type 1 (Th 1) response. We have chosen intratumor injection of ALVAC-hIL-12 and ALVAC-hB7.1 because the ALVAC vector can induce local lymphokine and co-stimulatory molecule expression with minimal systemic toxicity and a schedule of repeat administration to the same tumor site so that an extended period of IL-12 and B7.1 expression is feasible given the kinetics of ALVAC transgene expression observed in vitro. This phase I study will emphasize safety, confirmation of IL-12 and B7.1 expression within injected nodules, the local inflammatory response induced and anti-tumor effects. Patients will also be evaluated for evidence of humoral and cellular immune responses to melanoma-associated antigens. If promising results are observed in this initial study, a follow-up Phase II protocol will be written with less emphasis on toxicity monitoring and validation of transgene expression and more emphasis on immune response monitoring and evaluation of tumor regression.